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I, VIVIEN IRENE COULSON, declare:

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland, residing at 96 Langley Road, Watford, Hertfordshire, WD17 4PJ;
2. That I am well acquainted with the French and English languages;
3. That the attached is a true translation into the English language of the certified copy of French Patent Application No. 0008378 filed 29th June 2000;
4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the patent application in the United States of America or any patent issuing thereon.

Declared this

31st

day of

July 2001

V.I. Coulson

V.I. COULSON

FRENCH REPUBLIC
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Confirmation of a deposit by facsimile		<input type="checkbox"/> No. given by INPI to the facsimile	
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<i>Initial patent application or initial utility certificate application</i>		No.	Date
Conversion of a European Patent Application		No.	Date
<i>Initial patent application</i>		No.	Date
3 TITLE OF THE INVENTION (maximum 200 characters or spaces) NEW DIPHENYLUREA COMPOUNDS, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM			
4 DECLARATION OF PRIORITY OR REQUEST FOR THE BENEFIT OF THE FILING DATE OF A PRIOR FRENCH APPLICATION		Country or organisation Date No. Country or organisation Date No. Country or organisation Date No. <input type="checkbox"/> If there are other priorities, mark the box and use the "Continuation" form	
5 APPLICANT		<input type="checkbox"/> If there are other Applicants, mark the box and use the "Continuation" form	
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7 INVENTOR(S)			
The inventors are the Applicants		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No In this case, supply a separate declaration of inventorship	
8 SEARCH REPORT		For a patent application only (including division and conversion)	
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10 SIGNATURE OF THE APPLICANT OR OF THE AUTHORISED AGENT (Name and position of signatory) Nicolas RUIZ (Patent Engineer)		STAMP OF THE PREFECTURE OR OF THE INPI A. PAGNIER (signature)	

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DECLARATION OF INVENTORSHIP Page No. 1/2

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Your references for this file (<i>optional</i>)		35305	
NATIONAL REGISTRATION NO.		0008378	
TITLE OF THE INVENTION (maximum 200 characters or spaces) NEW DIPHENYLUREA COMPOUNDS, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM			
APPLICANT(S): ADIR ET COMPAGNIE 1 rue Carle Hébert 92415 COURBEVOIE CEDEX FRANCE			
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The present invention relates to new diphenylurea compounds, to a process for their preparation and to pharmaceutical compositions containing them.

The invention relates also to their use as mixed $\alpha_2/5$ -HT_{2c} ligands.

Compounds having a diphenylurea structure have been described in the Application
5 JP 11130750 for their serotonergic antagonistic properties, and in the Application WO 99 32436 for their use as raf kinase inhibitors.

The frontal cortex plays an essential role in the processes that control the functions affected in psychiatric disorders. In particular, it is now accepted that the disturbance of monoaminergic transmission is strongly implicated in the etiology of those various
10 disorders. For example, in the case of depression, monoaminergic activity is reduced in the corticolimbic regions.

Among the various monoamine auto- and hetero-receptor classes implicated in regulatory mechanisms, α_2 -A.R. receptors (autoreceptors) and 5-HT_{2c} receptors have proved to be of major importance. Those two receptor sub-types act in the same way by inhibiting
15 dopaminergic and adrenergic transmission. On the one hand a retrocontrol is exerted by α_2 -A.R. receptors on noradrenergic neurons (J. Pharmacol. Exp. Ther., 1994, 270, 958), and on the other hand 5-HT_{2c} receptors exert an inhibiting control on dopaminergic and noradrenergic transmission (Neuropharmacology, 1997, 36, 609).

In the past, compounds binding one or the other of those receptor sub-types have
20 demonstrated their potential in the treatment of a plurality of pathologies.

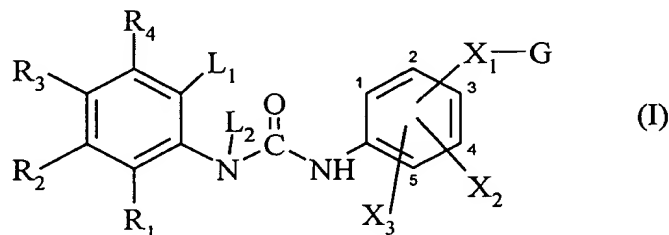
For example, the beneficial role of α_2 antagonist compounds has been studied in the treatment of cognitive disorders (J. Pharmacol., 1992, 6, 376), Parkinson's disease (CNS Drugs, 1998, 10, 189), libido disorders and sexual dysfunction (J. Pharmacol., 1997, 11, 72). Similarly, 5HT_{2c} receptor antagonist compounds have demonstrated their
25 usefulness in the treatment of sexual dysfunction (ref. J. Pharmacol., *ibid.*), Parkinson's

disease (Drug News Perspect., 1999, 12, 477), and also anxiety (Br. J. Pharmacol., 1996, 117, 427) and schizophrenia (Neurosci. Lett., 1996, 181, 65).

Compounds having a dual α_2 -A.R. and 5-HT_{2c} antagonist character may be of significant use for clinicians for achieving, with the administration of a single compound, an appreciably enhanced action in the restoration of neurotransmission by means of a synergistic effect. That kind of compound furthermore presents a considerable advantage in comparison with the administration of two different products.

The compounds of the invention have a novel structure that confers on them such a dual α_2 /5-HT_{2c} antagonist character, and they are accordingly useful in the treatment of depression, anxiety, schizophrenia, Parkinson's disease, cognitive disorders, libido disorders and sexual dysfunction, sleep disorders, drug abuse, and impulsive behaviour disorders.

The present invention relates to the compounds of formula (I) :



wherein :

- ✓ R₁, R₂, R₃ and R₄ independently represent a hydrogen atom, a halogen atom or an alkyl, alkoxy, hydroxy, cyano, amino (optionally substituted by one or two alkyl groups), nitro, carboxy, alkoxy carbonyl, aminocarbonyl (optionally substituted by one or two alkyl groups) or carbamoyl group,
- or, taken in pairs, form together with the carbon atoms to which they are bonded a phenyl ring or an aromatic heterocycle having from 5 to 7 ring members and containing from 1 to 3 hetero atoms selected from nitrogen, oxygen and sulphur,
- ✓ L₁ and L₂ each represents a hydrogen atom or together form a -CH₂-CH₂- group,

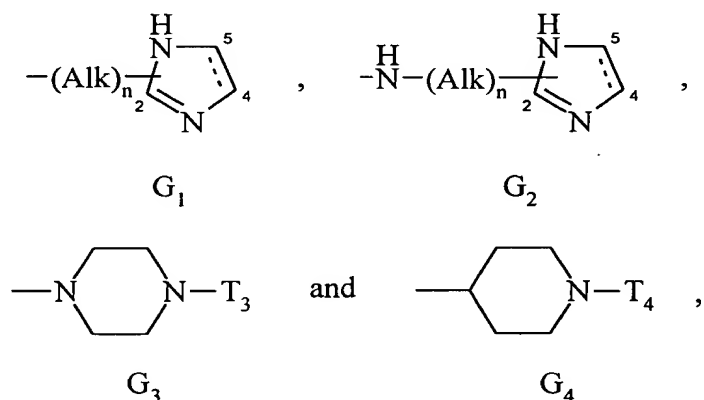
- ✓ X_1 , attached at the 2 or 3 position of the aromatic ring, represents a bond, and in that case X_2 represents a hydrogen atom, a halogen atom, an alkyl, alkoxy, hydroxy, nitro or cyano group or an amino group (optionally substituted by one or two alkyl groups),

5 or,

X_1 and X_2 , together with two adjacent carbon atoms to which they are bonded in the 2, 3 or 4 position of the aromatic ring, form a (C₅-C₇)cycloalkyl group,

- ✓ X_3 represents a hydrogen atom, a halogen atom, an alkyl, alkoxy, hydroxy, nitro or cyano group, or an amino group (optionally substituted by one or two alkyl groups),

- 10 ✓ G represents a group selected from :



wherein :

- ✓ the broken lines indicate the optional presence of a double bond,

- 15 ✓ Alk represents a linear or branched (C₁-C₆)alkylene group wherein, when G_1 or G_2 contains an imidazoline group, the group Alk- is attached at the 2 position of the ring,

- ✓ n is 0 or 1,

- 20 ✓ T_3 represents an alkyl, substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl group,

- ✓ T₄ represents an alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl group,

wherein :

- the term "alkyl" denotes a linear or branched group containing from 1 to 6 carbon atoms,
- the term "alkoxy" denotes a linear or branched alkyl-oxy group containing from 1 to 6 carbon atoms,
- the term "aryl" denotes a phenyl, naphthyl or biphenyl group,
- the term "heteroaryl" denotes an aromatic monocyclic group, or a bicyclic group in which at least one of the rings is aromatic, containing from 5 to 11 ring members and from 1 to 5 hetero atoms selected from nitrogen, oxygen and sulphur,
- the expression "optionally substituted" associated with the groups aryl, arylalkyl, heteroaryl and heteroarylalkyl denotes that those groups are unsubstituted or substituted on the cyclic moiety by one or more halogen atoms or groups alkyl, alkoxy, hydroxy, mercapto, alkylthio, cyano, amino (optionally substituted by one or two alkyl groups), nitro, carboxy, alkoxycarbonyl, aminocarbonyl (optionally substituted by one or two alkyl groups), carbamoyl, wherein the heteroaryl and heteroarylalkyl groups may in addition be substituted by an oxo group,

to enantiomers and diastereoisomers thereof, and also to addition salts thereof with a pharmaceutically acceptable acid or base.

Among the pharmaceutically acceptable acids there may be mentioned hydrochloric acid, hydrobromic acid, sulphuric acid, phosphonic acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, methanesulphonic acid, camphoric acid, etc..

Among the pharmaceutically acceptable bases there may be mentioned sodium hydroxide, potassium hydroxide, triethylamine, tert-butylamine, etc..

In preferred compounds of formula (I), R_1 and R_4 each represents a hydrogen atom.

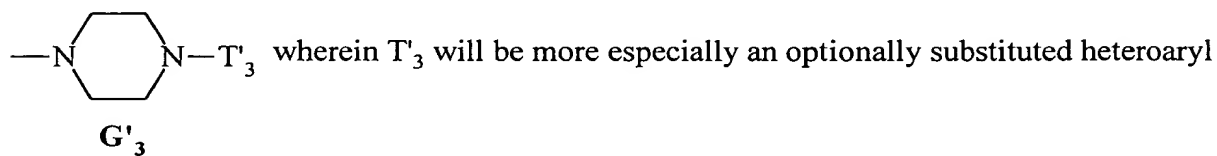
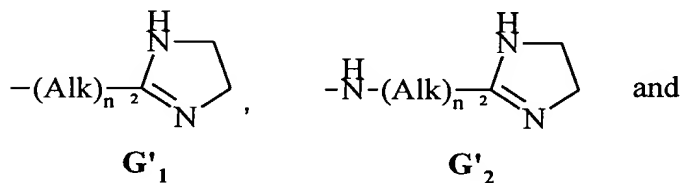
In compounds of formula (I), R_2 and R_3 are advantageously selected from a halogen atom and an alkyl group.

5 An advantageous embodiment of the invention relates to compounds of formula (I) wherein X_1 is attached at the 3 position of the phenyl ring.

Preferred compounds of the invention are those wherein X_1 represents a bond and X_2 represents a halogen atom or an alkyl or alkoxy group.

Another advantageous embodiment of the invention relates to compounds of formula (I) wherein X_3 represents a hydrogen atom.

10 In preferred compounds of formula (I), G will advantageously be selected from the groups



group or optionally substituted heteroarylalkyl group.

15 Other preferred compounds of the invention are those wherein X_1 and X_2 , together with the two carbons in the 2 and 3 positions of the aromatic ring to which they are bonded, form a (C_5-C_7) cycloalkyl group, for example a cyclopentyl group.

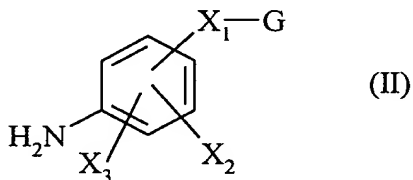
The aryl group preferred according to the invention is the phenyl group.

Among the preferred compounds of the invention, the following, more especially, may be mentioned :

- ♦ *N*-(3-chloro-4-methylphenyl)-*N'*-{3-[4-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1-piperazinyl]phenyl}urea,
- 5 ♦ *N*-[4-chloro-3-(4,5-dihydro-1*H*-imidazol-2-ylamino)phenyl]-*N'*-(3-chloro-4-methylphenyl)urea.

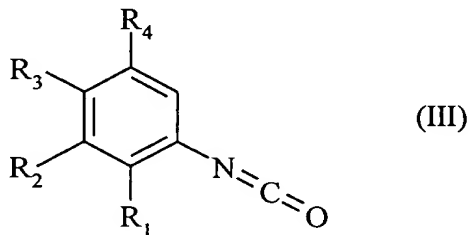
The invention extends also to a process for the preparation of the compounds of formula (I).

One process for the preparation of the compounds of formula (I) is characterised in that
10 there is used as starting material an aromatic amine of formula (II) :



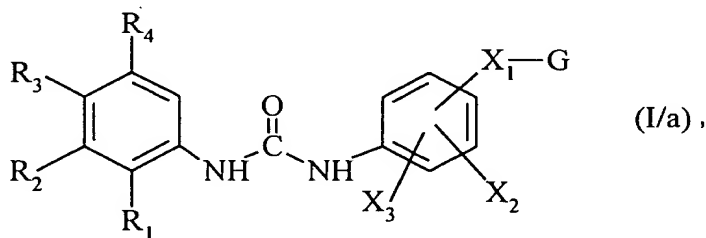
wherein X_1 , X_2 , X_3 and G are as defined for formula (I),

which is condensed by heating in basic medium with a compound of formula (III) :



15 wherein R_1 , R_2 , R_3 and R_4 are as defined for formula (I),

to yield the compound of formula (I/a) :



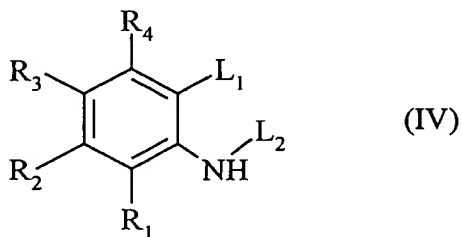
a particular case of the compounds of formula (I) wherein R_1 , R_2 , R_3 , R_4 , X_1 , X_2 , X_3 and G are as defined hereinbefore,

wherein the isocyanate of formula (III) is either commercially available or is prepared according to known procedures, for example from the corresponding carboxylic acid by
 5 reaction with sodium azide and rearrangement of the acyl azide obtained,

which compounds of formula (I/a)

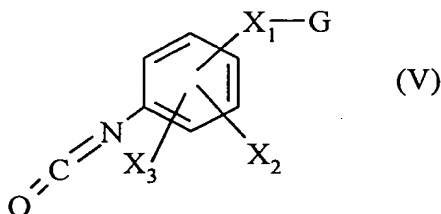
- may, if necessary, be purified according to a conventional purification technique,
- are optionally separated into isomers according to a conventional separation technique,
- 10 - are, if desired, converted into addition salts with a pharmaceutically acceptable acid or base.

Another process for the preparation of the compounds of formula (I) is characterised in that there is used as starting material an amine of formula (IV) :



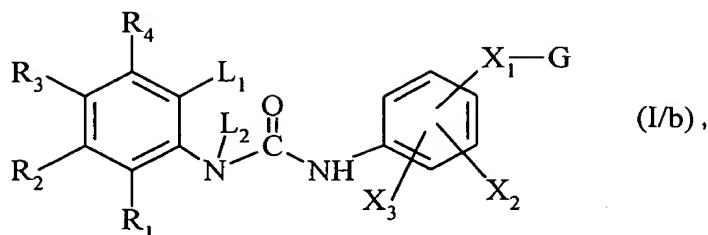
15 wherein L_1 , L_2 , R_1 , R_2 , R_3 and R_4 are as defined for formula (I),

which is condensed by heating in basic medium with a compound of formula (V) :



wherein X_1 , X_2 , X_3 and G are as defined for formula (I),

to yield the compound of formula (I/b) :



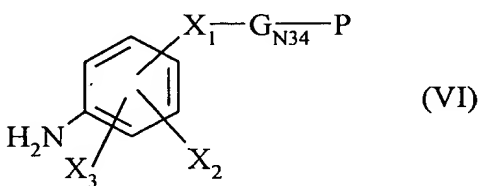
a particular case of the compounds of formula (I) wherein R_1 , R_2 , R_3 , R_4 , L_1 , L_2 , X_1 , X_2 , X_3 and G are as defined hereinbefore,

wherein the isocyanate of formula (V) is either commercially available or is prepared according to known procedures, for example from the corresponding carboxylic acid by reaction with sodium azide and rearrangement of the acyl azide obtained,

which compounds of formula (I/b)

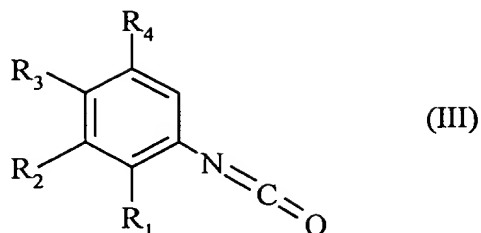
- may, if necessary, be purified according to a conventional purification technique,
- are optionally separated into isomers according to a conventional separation technique,
- are, if desired, converted into addition salts with a pharmaceutically acceptable acid or base.

Another process for the preparation of the compounds of formula (I) is characterised in that there is used as starting material an amine of formula (VI) :



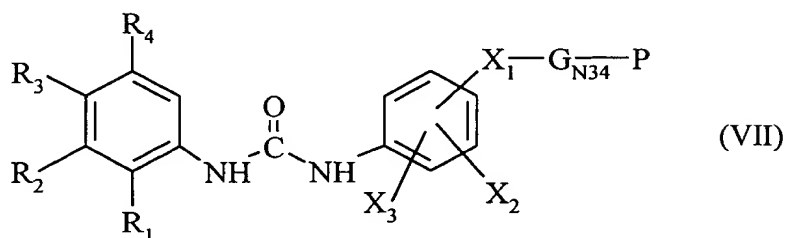
wherein X_1 , X_2 and X_3 are as defined for formula (I), G_{N34} represents an NH group or a 1-piperaziny1 or 4-piperidiny1 group, and P represents a hydrogen atom or a group protecting the amine function,

which is condensed by heating in basic medium with a compound of formula (III) :



wherein R_1 , R_2 , R_3 and R_4 are as defined for formula (I),

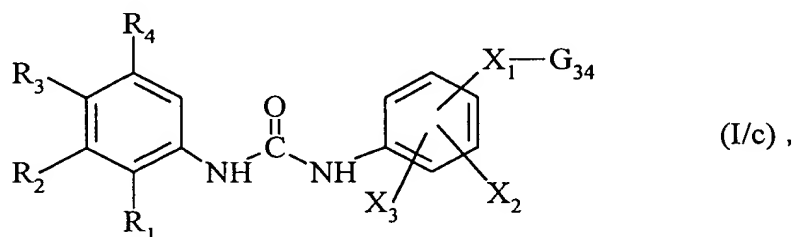
to yield the compound of formula (VII) :



5 wherein R_1 , R_2 , R_3 , R_4 , X_1 , X_2 , X_3 , G_{N34} and P are as defined hereinbefore,

which compound of formula (VII),

- when G_{N34} represents a 1-piperazinyl or 4-piperidinyl group, after deprotection where necessary of the amine function, is subjected to a substitution reaction in basic medium to yield the compound of formula (I/c) :

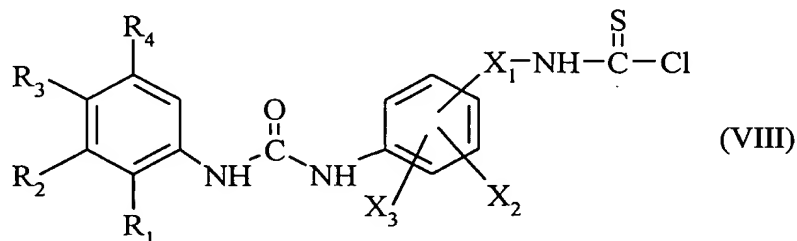


10

a particular case of the compounds of formula (I) wherein R_1 , R_2 , R_3 , R_4 , X_1 , X_2 and X_3 are as defined hereinbefore and G_{34} represents a group G_3 or G_4 as defined for formula (I),

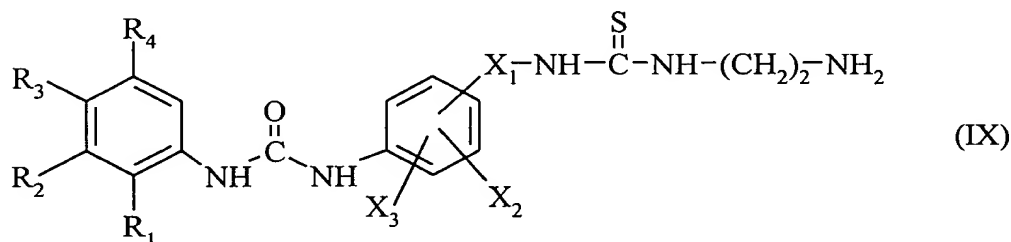
or

- when G_{N34} represents an NH group, after deprotection where necessary, is condensed with thiophosgene to yield the compound of formula (VIII) :



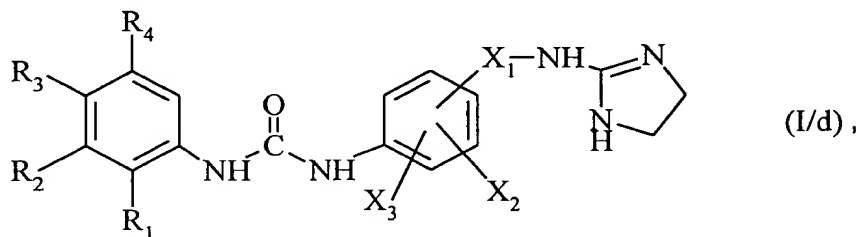
wherein R_1 , R_2 , R_3 , R_4 , X_1 , X_2 and X_3 are as defined hereinbefore,

- 5 which is subjected to the action of ethylenediamine to yield the compound of formula (IX):



wherein R_1 , R_2 , R_3 , R_4 , X_1 , X_2 and X_3 are as defined hereinbefore,

which compound of formula (IX) is subjected to an intramolecular cyclisation reaction catalysed by a palladium compound to yield the compound of formula (I/d) :



10 a particular case of the compounds of formula (I) wherein R_1 , R_2 , R_3 , R_4 , X_1 , X_2 and X_3 are as defined hereinbefore,

which compounds of formulae (I/c) and (I/d),

- may, if necessary, be purified according to a conventional purification technique,
- 15 - are optionally separated into isomers according to a conventional separation technique,

- are converted, if desired, into addition salts with a pharmaceutically acceptable acid or base.

The present invention relates also to pharmaceutical compositions comprising as active ingredient at least one compound of formula (I), alone or in combination with one or more pharmaceutically acceptable, inert, non-toxic excipients or carriers.

Among the pharmaceutical compositions according to the invention there may be mentioned more especially those which are suitable for oral, parenteral, nasal or transdermal administration, tablets or dragées, sublingual tablets, gelatine capsules, lozenges, suppositories, creams, ointments, dermal gels etc..

The useful dosage varies according to the age and weight of the patient, the nature and severity of the disorder and the administration route, which may be oral, nasal, rectal or parenteral. Generally, the unit dosage ranges from 0.05 mg to 500 mg for a treatment of from 1 to 3 administrations per 24 hours.

The following Examples illustrate the invention and do not limit it in any way. The structures of the compounds described were confirmed by customary spectroscopic techniques.

The starting materials used are known products or are prepared according to known procedures.

Preparation A : 3-(4,5-Dihydro-1H-imidazol-2-ylmethyl)aniline

Step 1 : 2-(3-Nitrobenzyl)-4,5-dihydro-1H-imidazole hydrochloride

A mixture of 30.7 mmol (5 g) of 3-nitrophenylacetonitrile and 30 mmol (7.2 g) of ethylenediamine para-toluenesulphonate is heated at 100°C for 1 hour. After cooling to 20°C, the mixture is hydrolysed with 100 ml of a 5M aqueous solution of sodium hydroxide and then extracted with dichloromethane. The organic phases are dried over

magnesium sulphate and concentrated. The residue obtained is converted into the hydrochloride by the action of an ethanolic HCl solution to yield the expected product.

Step 2 : *3-(4,5-Dihydro-1H-imidazol-2-ylmethyl)aniline*

5 A solution of 22.7 mmol (5.5 g) of the product described in the above Step in a mixture of 100 ml of ethanol and 10 ml of water is stirred under a hydrogen atmosphere in the presence of 0.5 g of 10 % palladium-on-carbon. When the absorption of hydrogen has ceased, the reaction mixture is filtered and concentrated to yield the expected product.

Preparation B : *3-[1-(4,5-Dihydro-1H-imidazol-2-yl)ethyl]aniline*

10 Step 1 : *2-(3-Nitrophenyl)propanenitrile*

15 A mixture of 62 mmol (10 g) of 3-nitrophenylacetonitrile, 1.11 mol (100 g) of dimethyl carbonate and 3.1 mmol (0.43 g) of potassium carbonate is heated for 6 hours at 170°C in an autoclave. After cooling, 200 ml of dichloromethane are added and the organic phase is washed with 100 ml of water and then with 100 ml of a saturated aqueous solution of sodium chloride. The organic phase is dried over magnesium sulphate and concentrated. The residue obtained is purified by chromatography on silica gel, using as eluant a 90/10 cyclohexane/ethyl acetate mixture, to yield the expected product.

Step 2 : *2-[1-(3-Nitrophenyl)ethyl]-4,5-dihydro-1H-imidazole*

20 The expected product is obtained in accordance with the procedure described in Preparation A, Step 1, using as starting material the compound described in the above Step.

Step 3 : *3-[1-(4,5-Dihydro-1H-imidazol-2-yl)ethyl]aniline*

25 The expected product is obtained in accordance with the procedure described in Preparation A, Step 2, using as starting material the compound described in the above Step.

Preparation C : 3-[1-(4,5-Dihydro-1H-imidazol-2-yl)-1-methylethyl]aniline

Step 1 : 2-Methyl-2-(3-nitrophenyl)propanenitrile

40 ml of 50 % sodium hydroxide solution are added to a vigorously stirred solution of
5 123 mmol (20 g) of 3-nitrophenylacetonitrile and 369 mmol (46.5 g) of dimethyl sulphate
in 200 ml of dimethyl sulphoxide. After stirring for one hour, the reaction mixture is
diluted with 2 litres of water and extracted twice with 1 litre of diethyl ether. The organic
phases are dried over sodium sulphate and concentrated to yield the expected product.

10 Step 2 : 2-[1-Methyl-1-(3-nitrophenyl)ethyl]-4,5-dihydro-1H-imidazole

The expected product is obtained in accordance with the procedure described in
Preparation A, Step 1, using as starting material the compound described in the above Step.

Step 3 : 3-[1-(4,5-Dihydro-1H-imidazol-2-yl)-1-methylethyl]aniline

15 The expected product is obtained in accordance with the procedure described in
Preparation A, Step 2, using as starting material the compound described in the above Step.

Preparation D : 4-Methyl-3-(4-methyl-1-piperazinyl)aniline

Step 1 : 4-(2-Methylphenyl)-1-piperazinecarbaldehyde

20 With vigorous stirring, 437 mmol (77 g) of 2-methylphenylpiperazine are added to a
solution of 415 mmol (61.3 g) of trichloroacetaldehyde in 400 ml of dibutyl ether. The
reaction mixture is heated at 80°C for 1 hour and, after cooling, concentrated to yield the
expected product.

Step 2 : *1-Methyl-4-(2-methylphenyl)piperazine*

A solution of 437 mmol (90 g) of the compound described in the above Step in 400 ml of tetrahydrofuran is added to a suspension of 568 mmol (21.6 g) of lithium tetrahydroaluminate in 300 ml of tetrahydrofuran. The reaction mixture is stirred for 12 hours at 50°C. After cooling, the reaction mixture is hydrolysed with 52.5 ml of water and then 48 ml of an aqueous 10 % sodium hydroxide solution and finally with 88.5 ml of water. The precipitate formed is filtered off over Celite and the filtrate is concentrated. The residue obtained is taken up in 200 ml of water and extracted 3 times with 250 ml of dichloromethane. The organic phase is dried over magnesium sulphate and concentrated to yield the expected product.

Step 3 : *1-Methyl-4-(2-methyl-5-nitrophenyl)piperazine hydrochloride*

416 mmol (64 g) of potassium nitrate in powder form are added to a solution of 347 mmol (100 g) of the hydrogen sulphate of the compound described in the above Step in 500 ml of concentrated sulphuric acid. Stirring is carried out for 5 hours, and the reaction mixture is poured onto 1200 g of ice and then neutralised with solid potassium carbonate and extracted 3 times with 500 ml of ethyl acetate. The organic phases are dried and concentrated to yield the expected product. The corresponding hydrochloride is obtained by the action of an ethanolic HCl solution.

Step 4 : *4-Methyl-3-(4-methyl-1-piperazinyl)aniline*

The expected product is obtained in accordance with the procedure described in Preparation A, Step 2, using as starting material the compound described in the above Step.

Preparation E : **3-[4-(2,3-Dihydro-1,4-benzodioxin-2-ylmethyl)-1-piperazinyl]-aniline**

Step 1 : *1-(2,3-Dihydro-1,4-benzodioxin-2-ylmethyl)-4-(3-nitrophenyl)-piperazine*

5 A solution of 54.2 mmol (10 g) of 2-chloromethyl-2,3-dihydro-1,4-benzodioxin, 54.2 mmol (9.2 g) of 3-nitrophenylpiperazine and 6 g of potassium hydrogen carbonate in 100 ml of methyl-4-pentanone is heated at reflux for 72 hours. After cooling, the reaction mixture is concentrated. The residue is taken up in 200 ml of water and extracted with 200 ml of dichloromethane. The organic phase is dried over magnesium sulphate,
10 concentrated and purified by chromatography on silica gel, using as eluant a 99/1/0.1 dichloromethane/methanol/ammonia mixture, to yield the expected product.

Step 2 : *3-[4-(2,3-Dihydro-1,4-benzodioxin-2-ylmethyl)-1-piperazinyl]aniline*

The expected product is obtained in accordance with the procedure described in Preparation A, Step 2, using as starting material the compound described in the above Step.

15 **Preparation F :** ***N*³-(4,5-Dihydro-1*H*-imidazol-2-yl)-4-methyl-1,3-benzenediamine**

Step 1 : *2-Methyl-5-nitrophenylcarbamoithioic acid chloride*

2.25 l of water are added to a solution of 130 mmol (20 g) of 2-methyl-5-nitroaniline in 375 ml of concentrated hydrochloric acid. At a temperature of 0°C, 162 mmol (19 g) of
20 thiophosgene are poured in in one go. The reaction mixture is stirred vigorously for 24 hours at ambient temperature. The precipitate formed is filtered off and then taken up in diethyl ether. The organic phase is washed with water, dried over magnesium sulphate and concentrated to yield the expected product.

Step 2 : *N*-(2-Aminoethyl)-*N'*-(2-methyl-5-nitrophenyl)thiourea

A solution of 123 mmol (24 g) of the compound described in the above Step in 1000 ml of toluene is heated to 60°C. 246 mmol (8.27 ml) of ethylenediamine are rapidly added and the mixture is heated at 100°C for 3 hours. After cooling, the organic phase is washed with
5 a 1M hydrochloric acid solution. The aqueous phase is rendered alkaline with concentrated sodium hydroxide solution and then extracted with dichloromethane. The organic phase is washed with water, dried over magnesium sulphate, concentrated and purified by chromatography on silica gel, using as eluant a 90/10/1 dichloromethane/methanol/-ammonia mixture, to yield the expected product.

10 Step 3 : *N*-(2-Methyl-5-nitrophenyl)-4,5-dihydro-1*H*-imidazol-2-amine

A hot solution of 38.8 g of potassium hydroxide in 135 ml of water is added at 50°C to a solution of 63 mmol (16.0 g) of the compound described in the above Step. With vigorous stirring, at 80°C, a hot solution of 72.5 mmol (27.2 g) of lead acetate in 135 ml of water is added. After 30 minutes, the reaction mixture is filtered over Celite and concentrated. The
15 residue is taken up in 100 ml of water and the pH is adjusted to 10. Following extraction with dichloromethane, the organic phase is dried over magnesium sulphate and concentrated to yield the expected product.

Step 4 : *N*³-(4,5-Dihydro-1*H*-imidazol-2-yl)-4-methyl-1,3-benzenediamine

The expected product is obtained in accordance with the procedure described in
20 Preparation A, Step 2, using as starting material the compound described in the above Step.

Preparation G : *N*¹-(4,5-Dihydro-1*H*-imidazol-2-yl)-1,3-benzenediamine

Step 1 : *N*-(3-Nitrophenyl)-4,5-dihydro-1*H*-imidazol-2-amine

The expected product is obtained in accordance with the procedure described in Preparation F, Step 2, using as starting material 3-nitrophenyl isothiocyanate.

Step 2 : *N'*-(4,5-Dihydro-1H-imidazol-2-yl)-1,3-benzenediamine

The expected product is obtained in accordance with the procedure described in Preparation A, Step 2, using as starting material the compound described in the above Step.

Preparation H : 2-Methoxy-5-(4-methyl-1-piperazinyl)benzoyl azide

5 A solution of 25 mmol (5.3 g) of phenyl dichlorophosphate in 100 ml of dichloromethane is added to a solution of 20 mmol (5 g) of 4-methoxy-3-(4-methyl-1-piperazinyl)benzoic acid (described in J. Med. Chem., 1994, 37, p.2255) and 50 mmol (3.25 g) of sodium azide in 4.05 ml of pyridine. After stirring for 12 hours at ambient temperature, the organic phase is washed with 100 ml of water, dried over magnesium sulphate and concentrated to yield
10 the expected product.

EXAMPLE 1 : N-(3-Chloro-4-methylphenyl)-N'-[3-(4,5-dihydro-1H-imidazol-2-ylmethyl)phenyl]urea hydrochloride

15 A solution of 4.7 mmol (1 g) of the compound described in Preparation A and 4.7 mmol (0.79 g) of 3-chloro-4-methylphenyl isocyanate in 50 ml of dimethylformamide is heated for 2 hours at 100°C. After cooling, the reaction mixture is concentrated. The residue obtained is taken up in 200 ml of dichloromethane, and the precipitate obtained is filtered off and purified by chromatography on silica gel, using as eluant a 90/10/1 dichloromethane/methanol/ammonia mixture, to yield the expected product. The corresponding hydrochloride is obtained by the action of an ethanolic HCl solution.

20 Melting point : 227-229°C

Elemental microanalysis : C₁₈H₁₉ClN₄O . HCl

	C	H	N	Cl
% Calculated :	57.00	5.31	14.77	9.35
% Found :	56.56	5.41	14.32	9.59

EXAMPLE 2 : *N*-(3-Chloro-4-methylphenyl)-*N'*-{3-[1-(4,5-dihydro-1*H*-imidazol-2-yl)ethyl]phenyl}urea hydrochloride

The expected product is obtained in accordance with the procedure described in Example 1, with replacement of the product described in Preparation A with the compound described in Preparation B.

Melting point : 100-102°C

Elemental microanalysis : C₁₉H₂₁ClN₄O . HCl

	C	H	N	Cl
% Calculated :	58.02	5.64	14.24	9.01
% Found :	58.07	5.95	13.55	8.91

EXAMPLE 3: *N*-(3-Chloro-4-methylphenyl)-*N'*-{3-[1-(4,5-dihydro-1*H*-imidazol-2-yl)-1-methylethyl]phenyl}urea hydrochloride

The expected product is obtained in accordance with the procedure described in Example 1, with replacement of the product described in Preparation A with the compound described in Preparation C.

Melting point : 232-233°C

Elemental microanalysis : C₂₀H₂₃ClN₄O . HCl

	C	H	N	Cl
% Calculated :	58.97	5.94	13.75	8.70
% Found :	58.32	6.11	13.13	9.11

EXAMPLE 4 : *N*-(3-Chloro-4-methylphenyl)-*N'*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]urea hydrochloride

A mixture of 13.6 mmol (3 g) of 4-methoxy-3-(4-methyl-1-piperazinyl)phenylamine and 13.6 mmol (2.26 g) of 3-chloro-4-methylphenyl isocyanate in 100 ml of toluene is heated at reflux for 2 hours. After cooling, the precipitate obtained is filtered off, and rinsed twice with diethyl ether. The solid obtained is purified by chromatography on silica gel, using as eluant a 96/4/0.4 dichloromethane/methanol/ammonia mixture, to yield the expected

product. The corresponding hydrochloride is obtained by the action of an ethanolic HCl solution.

Melting point : 206-208°C

Elemental microanalysis : $C_{20}H_{25}ClN_4O_2 \cdot HCl$

	C	H	N	Cl
% Calculated :	55.29	6.10	12.90	18.36
% Found :	55.59	6.14	12.70	18.31

5 **EXAMPLE 5 :** *N*-(3-Chloro-4-methylphenyl)-*N'*-[4-methyl-3-(4-methyl-1-piperazinyl)phenyl]urea hydrochloride

The expected product is obtained using the procedure described in Example 4, with the replacement of 4-methoxy-3-(4-methyl-1-piperazinyl)phenylamine with the compound described in Preparation D.

10 Melting point : 229-231°C

Elemental microanalysis : $C_{20}H_{25}ClN_4O \cdot HCl$

	C	H	N	Cl
% Calculated :	58.68	6.40	13.69	17.32
% Found :	58.16	6.37	13.20	17.16

EXAMPLE 6: *N*-(3-Chloro-4-methylphenyl)-*N'*-{3-[4-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1-piperazinyl]phenyl}urea hydrochloride

15 The expected product is obtained using the procedure described in Example 4, with the replacement of 4-methoxy-3-(4-methyl-1-piperazinyl)phenylamine with the compound described in Preparation E.

Melting point : 180-185°C

Elemental microanalysis : $C_{27}H_{29}ClN_4O_3 \cdot HCl$

	C	H	N	Cl
% Calculated :	57.30	5.53	9.90	18.79
% Found :	57.36	5.55	9.63	18.85

EXAMPLE 7: *N*-(3-Chloro-4-methylphenyl)-*N'*-[3-(4,5-dihydro-1*H*-imidazol-2-ylamino)-4-methylphenyl]urea hydrochloride

The expected product is obtained in accordance with the procedure described in Example 1, with replacement of the product described in Preparation A with the compound described in Preparation F.

Melting point : 252-254°C

Elemental microanalysis : C₁₈H₂₀ClN₅O . HCl

	C	H	N	Cl
% Calculated :	54.83	5.37	17.76	8.99
% Found :	54.91	5.25	17.78	9.12

EXAMPLE 8 : *N*-(3-Chloro-4-methylphenyl)-*N'*-[3-(4,5-dihydro-1*H*-imidazol-2-ylamino)phenyl]urea hydrochloride

The expected product is obtained in accordance with the procedure described in Example 1, with replacement of the product described in Preparation A with the compound described in Preparation G.

Melting point : 180-185°C

Elemental microanalysis : C₁₇H₁₈ClN₅O . HCl

	C	H	N	Cl
% Calculated :	53.01	5.10	18.14	10.38
% Found :	53.18	5.02	18.25	10.16

EXAMPLE 9 : *N*-[4-Chloro-3-(4,5-dihydro-1*H*-imidazol-2-ylamino)phenyl]-*N'*-(3-chloro-4-methylphenyl)urea hydrochloride

Step a : *N*-(3-Chloro-4-methylphenyl)-*N'*-(4-chloro-3-nitrophenyl)urea

A solution of 29.8 mmol (5 g) of 3-chloro-4-methylphenyl isocyanate in 90 ml of toluene is heated to 70°C, and 29.8 mmol (5.15 g) of 4-chloro-3-nitroaniline are poured in. The solution is heated at reflux for 24 hours. The reaction mixture is cooled using ice, and the

precipitate formed is filtered off and then rinsed with diethyl ether to yield the expected product.

Step b : *N*-(3-Amino-4-chlorophenyl)-*N'*-(3-chloro-4-methylphenyl)urea

A solution of 22.2 mmol (7.5 g) of the compound described in the above Step in 80 ml of a methanol/tetrahydrofuran mixture is heated to 45°C in the presence of Raney nickel. While controlling the temperature, 33.3 mmol (1.61 ml) of hydrazine hydrate are added. The temperature is maintained at 45°C for 30 minutes and a further 33.3 mmol (1.61 ml) of hydrazine hydrate is added. The mixture is stirred at reflux for 30 minutes. After cooling, the catalyst is filtered off and the filtrate is concentrated. The residue obtained is taken up in diethyl ether and washed to yield the expected product.

Step c : *2-Chloro-5-{[(3-chloro-4-methylanilino)carbonyl]amino}phenyl-carbamothioic acid chloride*

3.2 mmol (0.25 ml) of thiophosgene are added at 5°C to a suspension of 3.2 mmol (0.32 g) of calcium carbonate in a mixture of 15 ml of dichloromethane and 2.2 ml of water. At that temperature, 3.2 mmol (1 g) of the compound described in the above Step dissolved in dichloromethane are added. After the addition of 4.25 mmol (0.36 g) of sodium hydrogen carbonate, the reaction mixture is stirred for 15 minutes at ambient temperature. After filtration over Celite, the filtrate is decanted off and the organic phase is washed with water and then with a saturated aqueous solution of sodium chloride. After drying over magnesium sulphate and filtration, the filtrate is concentrated. The residue obtained is taken up in diethyl ether and washed to yield the expected product.

Step d : *N*-[3-({[(2-Aminoethyl)amino]carbothioyl}amino)-4-chlorophenyl]-*N'*-(3-chloro-4-methylphenyl)urea

4.4 mmol (0.27 ml) of ethylenediamine are rapidly added to a solution, heated to 60°C, of 2.2 mmol (0.78 g) of the compound described in the above Step in 35 ml of toluene. The reaction mixture is heated at 100°C for 3 hours. After cooling, the organic phase is washed

with a 1N hydrochloric acid solution (10 ml). The aqueous phase is rendered alkaline with concentrated sodium hydroxide solution and then extracted with dichloromethane. The organic phase is washed with water, dried over magnesium sulphate, filtered and concentrated. The residue obtained is purified by chromatography on silica gel, using as eluant a 90/10/1 dichloromethane/methanol/ammonia mixture, to yield the expected product.

Step e : *N-[4-Chloro-3-(4,5-dihydro-1H-imidazol-2-ylamino)phenyl]-N'-(3-chloro-4-methylphenyl)urea*

A hot solution of 16.5 mmol (1.5 g) of potassium hydroxide in 5.5 ml of water is added to a solution of 1.5 mmol (0.63 g) of the compound described in the above Step in 10 ml of ethanol at 50°C. With vigorous stirring at 80°C, a hot solution of 1.72 mmol (1.1 g) of lead acetate in 5.5 ml of water is added. After 30 minutes, the mixture is filtered over Celite and the filtrate is concentrated. The residue is taken up in 5 ml of water, the pH is adjusted to 10 and extraction is carried out with dichloromethane. The organic phase is dried over magnesium sulphate, concentrated and purified by chromatography on silica gel, using as eluant a dichloromethane/methanol/ammonia mixture, to yield the expected product. The corresponding hydrochloride is obtained by the action of an ethanolic HCl solution.

Melting point : 255-257°C

Elemental microanalysis : $C_{17}H_{17}Cl_2N_5O \cdot HCl$

	C	H	N	Cl
% Calculated :	49.23	4.37	16.89	25.65
% Found :	48.82	4.47	16.62	25.44

EXAMPLE 10 : *N*-(3-Chloro-4-methylphenyl)-*N'*-{3-[4-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1-piperazinyl]-4-methoxyphenyl}urea hydrochloride

Step a : 4-(5-{[(3-Chloro-4-methylanilino)carbonyl]amino}-2-methoxyphenyl)-1-piperazinecarboxylic acid tert-butanolate

A solution of 34.4 mmol (10 g) of 4-(5-amino-2-methoxyphenyl)piperazine-1-carboxylic acid tert-butanolate (described in J. Med. Chem., 1999, p.202) and 37.8 mmol (5.9 g) of 3-chloro-4-methylphenyl isocyanate in 150 ml of toluene is heated at reflux for 2 hours. The reaction mixture is concentrated, and the residue is taken up in 200 ml of 4N hydrochloric acid and then heated at reflux for 4 hours. After cooling, the precipitate formed is filtered off and treated with a 2N sodium hydroxide solution in order to regenerate the corresponding base.

Step b : *N*-(3-Chloro-4-methylphenyl)-*N'*-{3-[4-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1-piperazinyl]-4-methoxyphenyl}urea

A solution of 12.3 mmol (5 g) of the product described in the above Step in a mixture of 100 ml of acetonitrile and 100 ml of diethyl ketone is heated at reflux for 48 hours in the presence of 12.3 mmol (2.3 g) of 2-chloromethyl-2,3-dihydro-1,4-benzodioxin, 1.3 g of potassium hydrogen carbonate and 100 mg of potassium iodide. After cooling, the mixture is concentrated and the residue obtained is extracted with dichloromethane. The organic phase is dried, concentrated and purified by chromatography on silica gel, using as eluant a 97/3/0.3 dichloromethane/methanol/ammonia mixture, to yield the expected product. The corresponding hydrochloride is obtained by the action of an ethanolic HCl solution.

Melting point : 193-197°C

Elemental microanalysis : C₂₈H₃₁ClN₄O₄ . HCl

	C	H	N	Cl
% Calculated :	58.23	5.88	9.58	7.29
% Found :	58.95	5.72	9.82	8.08

EXAMPLE 11 : 6-Chloro-5-fluoro-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-1-indolinecarboxamide

A solution of 10.9 mmol (3 g) of the compound described in Preparation H in 100 ml of toluene is heated at reflux for 1 hour. After cooling to 20°C, a solution of 10.9 mmol (1.9 g) of 6-chloro-5-fluoroindoline in 200 ml of dichloromethane is added, and the reaction mixture is heated at reflux for one night. After returning to ambient temperature, the reaction mixture is concentrated and purified by chromatography on silica gel, using as eluant a 95/5/0.5 dichloromethane/methanol/ammonia mixture, to yield the expected product.

Melting point : 177-180°C

Elemental microanalysis : C₂₁H₂₄ClFN₄O₂

	C	H	N	Cl
% Calculated :	60.21	5.77	13.37	8.46
% Found :	59.15	6.05	12.82	8.85

PHARMACOLOGICAL STUDY

EXAMPLE A : Penile erection test in the rat

The test allows the evaluation of the capacity of pharmacological agents to inhibit penile erections caused by the administration of a 5-HT_{2c} selective agonist, RO 60-0175.

Male Wistar rats weighing from 120 to 140 g on the day of the experiment are placed individually into plexiglass observation boxes immediately after having been administered the test compound or the carrier. Thirty minutes later, the animals are administered RO 60-0175 (1.25 mg/kg, subcutaneous route) and the number of erections that occur during the 30 minutes that follow is counted.

Results : The compounds of the invention appear to be capable of inhibiting penile erections induced by the administration of the 5-HT_{2c} selective agonist. They accordingly

have an antagonist character in respect of 5-HT_{2c} receptors. By way of example, the inhibitory concentration 50 (IC₅₀) of the compound of Example 6 is 0.7 mg/kg.

EXAMPLE B : Test in the mouse of aggressiveness induced by isolation

5 The animals used are male CD-1 mice. On arrival, the mice are isolated in individual cages with free access to food and drink. After a period of isolation of one month, pairs of mice that are constant in their aggressiveness are selected by observation of the latent period, the number and the duration of attacks when they are placed in each other's presence.

10 The test takes place once a week. On the day of the test, each mouse of the pair of mice (resident mouse and intruder mouse) is given a subcutaneous injection of carrier (control animals) or of test product (treated animals) in a volume of 10 ml/kg. After 30 minutes, the intruder mouse is introduced into the cage of the resident mouse. The latent period of the first attack and the number and duration of attacks are then measured for a period of three minutes.

15 A product is considered as specifically anti-aggressive when it reduces the number and the duration of attacks at non-sedative doses.

Results : The compounds of the invention appear to reduce significantly the number and duration of attacks. By way of example, the inhibitory dose 50 (ID₅₀) of the compound of Example 6 is 2.5 mg/kg (subcutaneous administration).

EXAMPLE C : Marble-burying test in the mouse

20 This test allows evaluation of the capacity of pharmacological agents to inhibit the spontaneous marble-burying behaviour in mice, the inhibition being predictive of antidepressant and/or anti-impulsive action.

25 Male NMRI mice weighing from 20 to 25 g on the day of the experiment are placed individually in Macrolon boxes containing 5 cm of sawdust and covered with a perforated plexiglass plate. Twenty four "tiger's eye" glass marbles are evenly distributed on the

sawdust at the periphery of the box. At the end of 30 minutes' free exploration, the animals are removed from the box and the number of buried marbles is counted.

Results : The compounds of the invention appear to inhibit spontaneous marble-burying behaviour in mice. By way of example, the effective dose 50 (ED₅₀) of the compound of Example 6 is 0.4 mg/kg.

EXAMPLE D : Determination of the affinity for α_2 adrenergic receptors in the rat

The affinity was determined by competition experiments with [³H]-RX 821,002. Membranes are prepared from rat cerebral cortex and incubated in triplicate for 60 minutes at 22°C with 0.4 nM [³H]-RX 821,002 and the test compound in a final volume of 1.0 ml. The incubation buffer contains 50 nM Tris-HCl (pH 7.5), 1 mM EDTA and 100 μ M GppNHp. Non-specific binding is determined using 10 μ M phentolamine.

Data analysis : At the end of the incubation, the incubation medium is filtered across WHATMAN GF/B filters impregnated with 0.1 % polyethylenimine and washed three times with 5 ml of cooled buffer. The radioactivity retained on the filters is determined by liquid scintillation counting. The binding isotherms are analysed by non-linear regression.

Results : The compounds of the invention exhibit an antagonist activity specific for α_2 -adrenergic receptors, for example a pKi of 6.7 for the compound of Example 6.

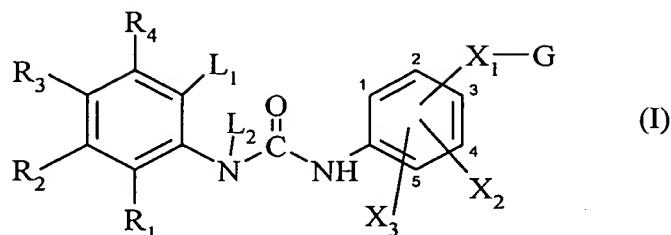
EXAMPLE E : Pharmaceutical composition

Formulation for the preparation of 1000 tablets each containing 10 mg of active ingredient

	compound of Example 6	10 g
	hydroxypropyl cellulose	2 g
	wheat starch	10 g
	lactose	100 g
5	magnesium stearate	3 g
	talc	3 g

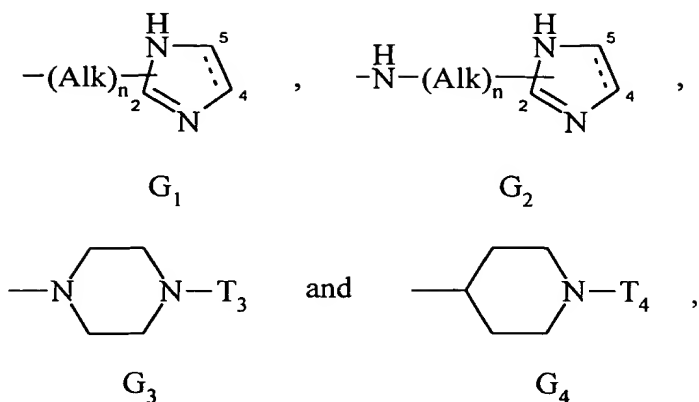
CLAIMS

1. Compounds of formula (I) :



wherein

- ✓ R_1 , R_2 , R_3 and R_4 independently represent a hydrogen atom, a halogen atom or an alkyl, alkoxy, hydroxy, cyano, amino (optionally substituted by one or two alkyl groups), nitro, carboxy, alkoxycarbonyl, aminocarbonyl (optionally substituted by one or two alkyl groups) or carbamoyl group,
or, taken in pairs, form together with the carbon atoms to which they are bonded a phenyl ring or an aromatic heterocycle having from 5 to 7 ring members and containing from 1 to 3 hetero atoms selected from nitrogen, oxygen and sulphur,
- ✓ L_1 and L_2 each represents a hydrogen atom or together form a $-CH_2-CH_2-$ group,
- ✓ X_1 , attached at the 2 or 3 position of the aromatic ring, represents a bond, and in that case X_2 represents a hydrogen atom, a halogen atom, an alkyl, alkoxy, hydroxy, nitro or cyano group or an amino group (optionally substituted by one or two alkyl groups),
or,
 X_1 and X_2 , together with two adjacent carbon atoms to which they are bonded in the 2, 3 or 4 position of the aromatic ring, form a (C_5-C_7) cycloalkyl group,
- ✓ X_3 represents a hydrogen atom, a halogen atom, an alkyl, alkoxy, hydroxy, nitro or cyano group, or an amino group (optionally substituted by one or two alkyl groups),
- ✓ G represents a group selected from :



wherein :

- ✓ the broken lines indicate the optional presence of a double bond,
- 5 ✓ Alk represents a linear or branched (C₁-C₆)alkylene group wherein, when G₁ or G₂ contains an imidazoline group, the group Alk- is attached at the 2 position of the ring,
- ✓ n is 0 or 1,
- ✓ T₃ represents an alkyl, substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl group,
- 10 ✓ T₄ represents an alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl group,

wherein :

- the term "alkyl" denotes a linear or branched group containing from 1 to 6 carbon atoms,
- 15 – the term "alkoxy" denotes a linear or branched alkyl-oxy group containing from 1 to 6 carbon atoms,
- the term "aryl" denotes a phenyl, naphthyl or biphenyl group,

- the term "heteroaryl" denotes an aromatic monocyclic group, or a bicyclic group in which at least one of the rings is aromatic, containing from 5 to 11 ring members and from 1 to 5 hetero atoms selected from nitrogen, oxygen and sulphur,
- the expression "optionally substituted" associated with the groups aryl, arylalkyl, heteroaryl and heteroarylalkyl denotes that those groups are unsubstituted or substituted on the cyclic moiety by one or more halogen atoms or groups alkyl, alkoxy, hydroxy, mercapto, alkylthio, cyano, amino (optionally substituted by one or two alkyl groups), nitro, carboxy, alkoxycarbonyl, aminocarbonyl (optionally substituted by one or two alkyl groups), carbamoyl, wherein the heteroaryl and heteroarylalkyl groups may in addition be substituted by an oxo group,

enantiomers and diastereoisomers thereof, and also addition salts thereof with a pharmaceutically acceptable acid or base.

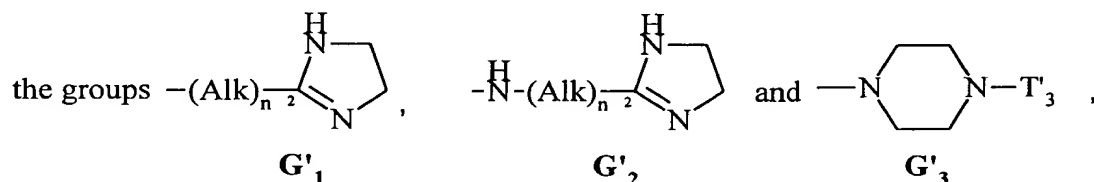
2. Compounds of formula (I) according to claim 1, wherein L_1 and L_2 each represents a hydrogen atom, enantiomers and diastereoisomers thereof, and also addition salts thereof with a pharmaceutically acceptable acid or base.
3. Compounds of formula (I) according to claim 1, wherein L_1 and L_2 together form a $-CH_2-CH_2-$ group, enantiomers and diastereoisomers thereof, and also addition salts thereof with a pharmaceutically acceptable acid or base.
4. Compounds of formula (I) according to claim 1, wherein R_1 and R_4 each represents a hydrogen atom, enantiomers and diastereoisomers thereof, and also addition salts thereof with a pharmaceutically acceptable acid or base.
5. Compounds of formula (I) according to claim 1, wherein R_2 and R_3 are selected from a halogen atom and an alkyl group, enantiomers and diastereoisomers thereof, and also addition salts thereof with a pharmaceutically acceptable acid or base.

6. Compounds of formula (I) according to claim 1, wherein X_1 is attached at the 3 position of the phenyl ring, enantiomers and diastereoisomers thereof, and also addition salts thereof with a pharmaceutically acceptable acid or base.

7. Compounds of formula (I) according to claim 1, wherein X_1 represents a bond and X_2 represents a halogen atom or an alkyl or alkoxy group, enantiomers and diastereoisomers thereof, and also addition salts thereof with a pharmaceutically acceptable acid or base.

8. Compounds of formula (I) according to claim 1, wherein X_3 represents a hydrogen atom, enantiomers and diastereoisomers thereof, and also addition salts thereof with a pharmaceutically acceptable acid or base.

9. Compounds of formula (I) according to claim 1, wherein G is selected from



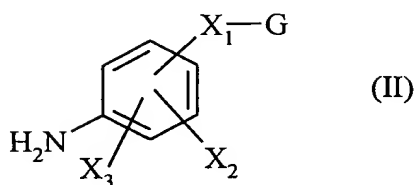
enantiomers and diastereoisomers thereof, and also addition salts thereof with a pharmaceutically acceptable acid or base.

10. Compounds of formula (I) according to claim 1, wherein X_1 and X_2 , together with the two carbon atoms in the 2 and 3 position of the aromatic ring to which they are bonded, form a (C_5-C_7) cycloalkyl group, enantiomers and diastereoisomers thereof, and also addition salts thereof with a pharmaceutically acceptable acid or base.

11. Compound of formula (I) that is *N*-(3-chloro-4-methylphenyl)-*N'*-{3-[4-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1-piperazinyl]phenyl}urea.

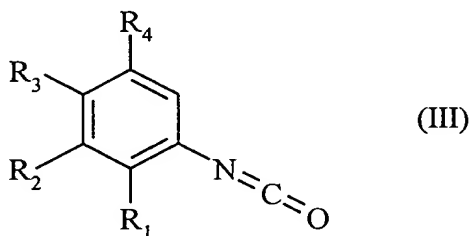
12. Compound of formula (I) that is *N*-[4-chloro-3-(4,5-dihydro-1*H*-imidazol-2-ylamino)-phenyl]-*N'*-(3-chloro-4-methylphenyl)urea.

13. Process for the preparation of the compounds of formula (I) according to claim 1, characterised in that there is used as starting material an aromatic amine of formula (II) :



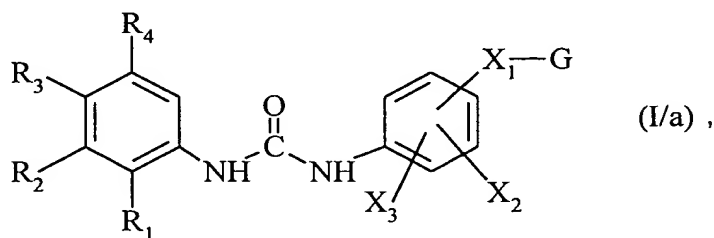
wherein X_1 , X_2 , X_3 and G are as defined for formula (I),

which is condensed by heating in basic medium with a compound of formula (III) :



wherein R_1 , R_2 , R_3 and R_4 are as defined for formula (I),

to yield the compound of formula (I/a) :



a particular case of the compounds of formula (I) wherein R_1 , R_2 , R_3 , R_4 , X_1 , X_2 , X_3 and G are as defined hereinbefore,

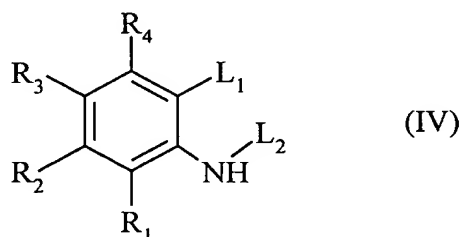
wherein the isocyanate of formula (III) is either commercially available or is prepared according to known procedures,

which compounds of formula (I/a)

– may, if necessary, be purified according to a conventional purification technique,

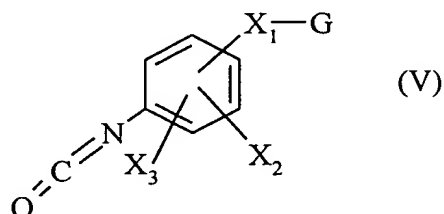
- are optionally separated into isomers according to a conventional separation technique,
- are, if desired, converted into addition salts with a pharmaceutically acceptable acid or base.

5 14. Process for the preparation of the compounds of formula (I) according to claim 1, characterised in that there is used as starting material an amine of formula (IV) :



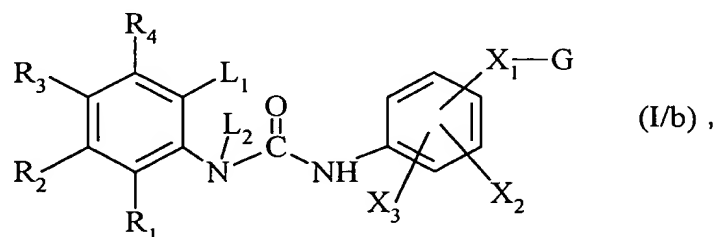
wherein L_1 , L_2 , R_1 , R_2 , R_3 and R_4 are as defined for formula (I),

which is condensed by heating in basic medium with a compound of formula (V) :



10 wherein X_1 , X_2 , X_3 and G are as defined for formula (I),

to yield the compound of formula (I/b) :



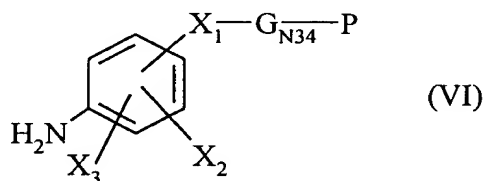
15 a particular case of the compounds of formula (I) wherein R_1 , R_2 , R_3 , R_4 , L_1 , L_2 , X_1 , X_2 , X_3 and G are as defined hereinbefore,

wherein the isocyanate of formula (V) is either commercially available or is prepared according to known procedures,

which compounds of formula (I/b)

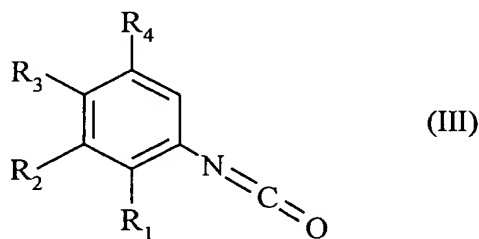
- may, if necessary, be purified according to a conventional purification technique,
- are optionally separated into isomers according to a conventional separation technique,
- are, if desired, converted into addition salts with a pharmaceutically acceptable acid or base.

15. Process for the preparation of the compounds of formula (I) according to claim 1, characterised in that there is used as starting material an amine of formula (VI) :



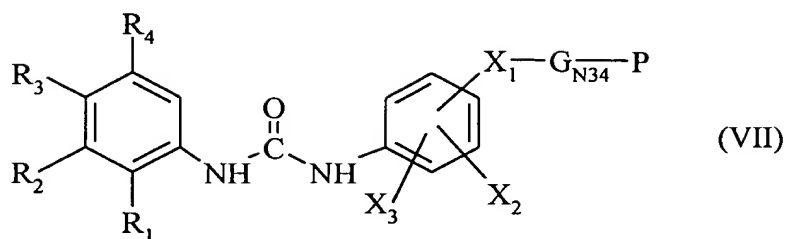
wherein X_1 , X_2 and X_3 are as defined for formula (I), G_{N34} represents an NH group or a 1-piperazinyl or 4-piperidinyl group, and P represents a hydrogen atom or a group protecting the amine function,

which is condensed by heating in basic medium with a compound of formula (III) :



wherein R_1 , R_2 , R_3 and R_4 are as defined for formula (I),

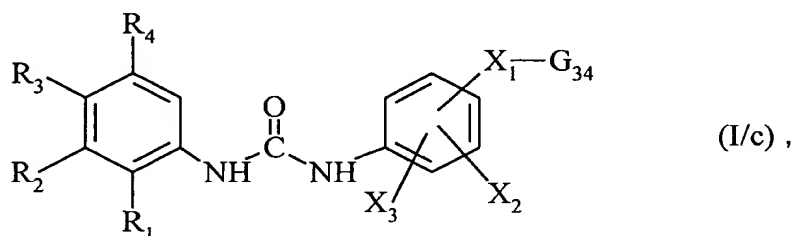
to yield the compound of formula (VII) :



wherein R_1 , R_2 , R_3 , R_4 , X_1 , X_2 , X_3 , G_{N34} and P are as defined hereinbefore,

which compound of formula (VII),

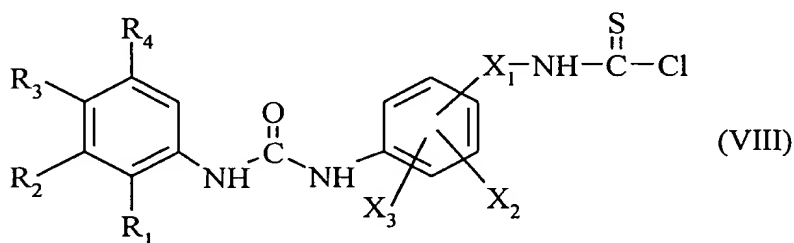
- when G_{N34} represents a 1-piperazinyl or 4-piperidinyl group, after deprotection where necessary of the amine function, is subjected to a substitution reaction in basic medium to yield the compound of formula (I/c) :



a particular case of the compounds of formula (I) wherein R_1 , R_2 , R_3 , R_4 , X_1 , X_2 and X_3 are as defined hereinbefore and G_{34} represents a group G_3 or G_4 as defined for formula (I),

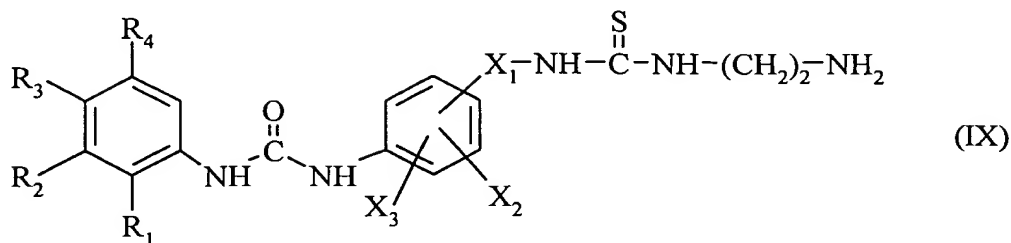
or

- when G_{N34} represents an NH group, after deprotection where necessary, is condensed with thiophosgene to yield the compound of formula (VIII) :



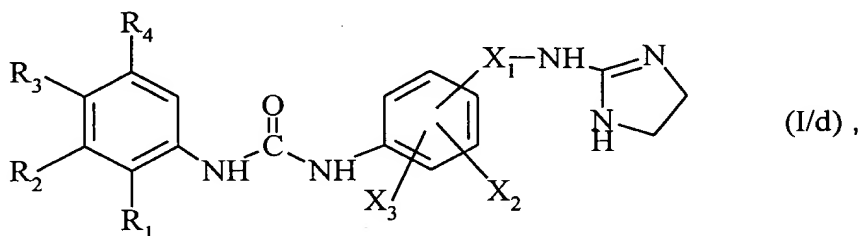
wherein R_1 , R_2 , R_3 , R_4 , X_1 , X_2 and X_3 are as defined hereinbefore,

which is subjected to the action of ethylenediamine to yield the compound of formula (IX):



wherein R_1 , R_2 , R_3 , R_4 , X_1 , X_2 and X_3 are as defined hereinbefore,

5 which compound of formula (IX) is subjected to an intramolecular cyclisation reaction catalysed by a palladium compound to yield the compound of formula (I/d) :



a particular case of the compounds of formula (I) wherein R_1 , R_2 , R_3 , R_4 , X_1 , X_2 and X_3 are as defined hereinbefore,

10 which compounds of formulae (I/c) and (I/d),

- may, if necessary, be purified according to a conventional purification technique,
 - are optionally separated into isomers according to a conventional separation technique,
 - are converted, if desired, into addition salts with a pharmaceutically acceptable acid or base.
- 15

16. Pharmaceutical compositions comprising as active ingredient at least one compound according to any one of claims 1 to 12, alone or in combination with one or more pharmaceutically acceptable, inert, non-toxic excipients or carriers.

17. Pharmaceutical compositions according to claim 16, containing at least one active ingredient according to any one of claims 1 to 12, for use in the preparation of

20

medicaments useful as dual $\alpha_2/5\text{-HT}_{2c}$ antagonists in the treatment of depression, anxiety, schizophrenia, Parkinson's disease, cognitive disorders, libido disorders, sexual dysfunction, sleep disorders, drug abuse and impulsive behaviour disorders.